Acute Kidney Injury for the General Surgeon

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Acute Kidney Injury: Epidemiology

- Acute ischemic renal injury is seen after all types of surgery, including cardiac, vascular, urologic, transplant and general surgery;
- AKI occurs in ~1% of all non-cardiac surgery patients who had normal preoperative renal function, with 0.1% requiring renal replacement therapy (Anesthesiology 2007;107:892-902);
- Postoperative acute kidney injury (AKI) accounts for 18-47% of all hospital-acquired AKI;
- An important source of increased length of stay, healthcare costs and mortality since AKI is associated with higher rates of GI bleeding, pneumonia and sepsis;
- The clinical manifestations can range from short periods of oliguria to the need for renal replacement therapy.

Acute Kidney Injury: Definition

In 2006, an international consensus definition for AKI based on GFR, creatinine and urine output, consisting of 3 grades & 2 outcome classes, was validated and shown to be associated with hospital mortality (Crit Care 2006;10:R73):

**Risk**
- Oliguria (<0.5 ml/kg/h) >6 h or increase in serum creatinine (Scr) >50%

**Injury**
- Oliguria >12 h or increase in Scr >100%

**Failure**
- Anuria >12 h or increase in Scr >200%

**Loss**
- Renal Replacement Therapy for > 4 weeks

**End stage renal disease**
- > 3 months
Acute Kidney Injury: Definition

- Acute kidney injury occurred in 67% of intensive care unit admissions, with maximum RIFLE class R, class I and class F in 12%, 27% and 28%, respectively;
- Patients with maximum RIFLE class R, class I and class F had hospital mortality rates of 9%, 11% and 26%, respectively, compared with <6% for patients without AKI;
- Study was confined to patients admitted to the ICU, so its implications for patients with AKI, not admitted to the ICU is uncertain;
- RIFLE classification system was modified in 2007 to include only grades of acute renal injury (Risk, Injury & Failure), in part to include a broader spectrum of ARI, and not include the need for therapy (RRT) for ARI as a distinct stage since this is an outcome and is variably applied (Crit Care 2007:11;R3).
Importantly, a rise in creatinine is a relatively insensitive measure of ARI, with its serum concentration not changing until ~50% renal function has been lost. Since early diagnosis improves outcome, new biomarkers have been proposed;

- The most promising new biomarker is neutrophil gelatinase-associated lipocalin (NGAL), a 25-kDa protein expressed by neutrophils and various epithelial cells, including proximal convoluted tubule cells, that is released within 2 h of acute injury;

- A recent meta-analysis (Am J Kidney Dis 2009;54:1012-1024) demonstrated the usefulness of NGAL as a diagnostic and prognostic tool in cardic surgery, ICU and contrast-induced nephropathy patients.

Unfortunately, NGAL may not be answer for the early detection of ARI in non-cardiac surgical patients.

Investigators examined the ability of urinary and serum NGAL to predict complications and mortality after non-cardiac major surgery (Kidney Blood Pressure Res 2011;34:116-124);

- AKI, postoperative infections and mortality were studied in 74 patients undergoing orthopedic, vascular and abdominal surgery lasting >2 hours;

Ten patients (13.5%) developed AKI;
- No significant correlation was detected between serum or urine NGAL and the development of AKI, but were strongly correlated with postoperative infection and death (p<0.014).

Underlying mechanisms are multifactorial:
- hemodynamic
- immunoinflammatory
- nephrotoxic

- An inflammatory condition that involves;
  - endothelial cell injury 
  - leukocyte infiltration 
  - release of soluble mediators of inflammation (cytokines, ROS)

Inflammation includes:
- endothelial cell activation and damage/loss 
- increased leukocyte adhesion to activated endothelial cells 
- leukocyte extravasation & entrapment 
- compromise in microvascular flow
Acute Kidney Injury: Pathophysiology

Prerenal Pathology secondary to decreased renal perfusion leading to a decrease in glomerular filtration rate (GFR); reversible if factors decreasing perfusion are corrected; otherwise, it can progress to an intrarenal pathology known as ischemic ATN.

Renal Pathology secondary to pathology within the kidney; acute tubular necrosis (ATN) is the most common cause via ischemic or nephrotoxic injury to the kidney; 75% of ATN is a complication of prerenal etiology.

Postrenal Pathology secondary to extrinsic or intrinsic obstruction of the urinary collection system.

Acute Kidney Injury: Clinical Studies

Hou et al – prospective review of hospital-acquired AKI

Examined 2,216 consecutive medical and surgical admissions to Tufts/NEMC followed for AKI – overall 5% had AKI

Etiologies:
- decreased renal perfusion (42%)
- major surgery (18%)
- contrast nephropathy (12%)
- aminoglycoside Abx (7%)

Crude in-hospital mortality 32%

Degree of renal injury (rise in SCr) was an important predictor
- in-hospital mortality with an increase in SCr 0.5-0.9 mg/dl: 3.8%
- in-hospital mortality with a Scr >3.0 mg/dl: 64%
- oliguria corresponded with mortality in pts with AKI (52% vs. 17% without)

TABLE IX: Impact of the Magnitude of the Increase in Serum Creatinine Concentration on Outcome

<table>
<thead>
<tr>
<th>Increase in Serum Creatinine (mg/dl)</th>
<th>Episodes of Renal Mortality (No.)</th>
<th>% of Patients Who Died</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5-0.9</td>
<td>83</td>
<td>7 (8.5%)</td>
</tr>
<tr>
<td>1.0-1.9</td>
<td>27</td>
<td>9 (40.7%)</td>
</tr>
<tr>
<td>2.0-2.9</td>
<td>14</td>
<td>5 (35.7%)</td>
</tr>
<tr>
<td>2.0-3.0</td>
<td>7</td>
<td>3 (42.9%)</td>
</tr>
<tr>
<td>3.0-4.0</td>
<td>8</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td>4.0 without dialysis</td>
<td>10</td>
<td>5 (50.0%)*</td>
</tr>
<tr>
<td>4.0 with dialysis</td>
<td></td>
<td>7 (70.0%)*</td>
</tr>
<tr>
<td>Total</td>
<td>129</td>
<td>22 (17.2%)</td>
</tr>
</tbody>
</table>

* Two patients required long-term dialysis.
**Acute Kidney Injury: Clinical Studies**

Program to Improve Care in Acute Renal Disease (PICARD) – observational cohort study of 618 with acute renal failure in the ICU at five academic medical centers in the US (Kidney International 2004;66:1613-1621)

Found significant differences across centers with respect to the use of Renal Replacement Therapy & clinical outcome;

In-hospital mortality ranged from 24 - 62%;

Common causes:
- ATN (no specific cause): 55%
- nephrotoxin: 26%
- cardiac disease: 20%
- sepsis: 19%
- pre-renal azotemia: 16%
- hepatorenal syndrome: 11%

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**Acute Kidney Injury: Clinical Studies**

Relatively small changes in renal function are more clinically relevant than commonly considered;

These data indicate that any major complication (including AKI) within 30 days of surgery is more important than preoperative risks and intraoperative factors in determining short- and long-term survival;

The etiologies of and patient outcomes from AKI are broad and vary among institutions, in part, potentially reflective of differences in management;

More multi-institutional trials are needed with a focus on identifying optimal diagnostic and therapeutic paradigms.

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**Acute Kidney Injury: Management**

- There are no evidence-based strategies for preventing AKI;
- A recent systematic review identified no reliable evidence that dopamine, diuretics, calcium channel blockers or ACE inhibitors can protect the kidneys during surgery (Cochrane Database Sys Rev 2005;CD003590);
- Fluid therapy: most cases of postoperative AKI are related to perioperative renal hypoperfusion from hypotension, hypovolemia and/or cardiac dysfunction. However, there is no RCT that has directly addressed the role of fluid resuscitation in preventing postoperative AKI;
- Perioperative Goal-directed Therapy: shown to improve outcomes in high-risk surgical patients, including decreased incidence of AKI. The goal is prevent tissue oxygen debt by maintaining tissue perfusion. Traditional measures of heart rate, blood pressure, central venous pressure and urine output are neither predictive nor able to be routinely manipulated to improve outcome. Alternatively, optimize global oxygen delivery (DO$_2$) via maintaining a cardiac index (CI) = 4.5 l/min/m$^2$ and tissue oxygen delivery (DO$_2$t) > 600 ml/min/m$^2$ through the use of fluids, blood and inotropes.
Acute Kidney Injury: Management

- **Choice of Intravenous Fluids:** the debate between crystalloid versus colloid resuscitation continues with no clear evidence supporting one approach over the other with respect to renal protection;

- **Pharmacologic Interventions:**
  - Fenoldopam mesylate, a dopamine 1 (DA-1) receptor agonist with no effects on DA-2 or α-1 receptors, increases both medullary and cortical blood flows and reduces renal oxygen demand.
    - meta-analysis of 1,290 patients revealed a reduced need for RRT and in-hospital mortality, but the study involved only 328 noncardiac surgery patients. More studies are needed;
  - Atrial Natriuretic Peptide may counteract the initiation phase of AKI by vasodilatation of the preglomerular artery and inhibition of the renin-angiotensin axis.

- **Tight Glucose Control:** the overall benefit of maintaining the serum glucose between 80-110 mg/dl is controversial with mixed clinical research findings. However, there is provocative animal data indicating that hyperglycemia exacerbates ischemia-reperfusion injury of the kidney.

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Acute Kidney Injury: Summary

- Acute Kidney Injury is common, impacting 1% of all surgical patients with normal preoperative renal function and ~10% of noncardiac surgical patients admitted to the ICU;

- Relatively small increases in serum creatinine predict significant morbidity and mortality;

- New biomarkers for the early diagnosis of AKI are under investigation, of which neutrophil gelatinase-associated lipocalin (NGAL) is the most promising;

- Goal-directed therapy is of demonstrated benefit in preventing AKI in high-risk surgical patients;

- New pharmacologic strategies for providing renal protection are aimed at improved blood flow to the kidney, but are still under clinical study;

- The value of tight glucose control is unclear.